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The effect of bilateral and unilateral knee arthroplasty under regional anesthesia on ischaemia-modified albumin and thiol/disulphide homeostasis

Knee arthroplasty and ischaemia reperfusion

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Abstract

Aim: Tourniquet application in extremity surgery causes ischemia-reperfusion injury. An increase in ischemia-modified albumin level is an early indicator of ischemia. The aim of this study is to investigate the effect of bilateral and unilateral total knee arthroplasty on the oxidation parameters and ischemia-modified albumin level, and thiol/disulfide homeostasis.

Material and Methods: A total of 57 patients who underwent knee arthroplasty were included in the study. Patients were divided into two groups: group 1 with unilateral knee arthroplasty (n=33) and group 2 with bilateral knee arthroplasty (n=24). Sociodemographic features, ischemia-modified albumin levels, and thiol/disulphide homeostasis were evaluated.

Results: Ischemia-modified albumin levels at the 5th minute and 24th hour were significantly higher in the bilateral arthroplasty group compared to its pre-operative level (p=0.001 and p=0.01, respectively). In the unilateral group, ischemia-modified albumin was significantly higher only in postoperative 24th hour compared to preoperative levels (p=0.012). In the intergroup comparison, only the ischemia modified albumin value at 5 minutes was high in the bilateral group (p=0.002). The hospital stay in Group 2 was significantly longer than that of patients in Group 1 (p=0.035).

Discussion: In cases of bilateral knee arthroplasty with spinal-epidural anesthesia, preoperative thiol/disulfide homeostasis parameters and ischemia-modified albumin values did not differ at the postoperative 24th hour.

Keywords

Regional anesthesia; Knee arthroplasty; Bilaterally; Modified albumin; Thiol

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Introduction

Osteoarthritis is a chronic degenerative disease with a high prevalence and costly treatment, especially involving load-bearing joints with pain, deformity, limited range of movement, and functional loss [1,2]. Most of the patients with osteoarthritis of the knee have symmetrical involvement, which requires bilateral surgery [3,4]. Total knee arthroplasty (TKA) is a frequent intervention in cases not responding to conservative treatment [5]. TKA can be performed on both knees simultaneously or in separate attempts [6-8]. Although simultaneous bilateral operation under a single anesthesia session has the advantages of lowering overall costs, shortening hospital stay, and better rehabilitation, the subject is under debate concerning the importance of patient selection [9,10].

Reperfusion after the ischemia incurred by TKA gives rise to protein fragmentation and changes in protein metabolism including protein synthesis inhibition [11]. Protein oxidation by the reactive derivatives, aromatic amino acids and thiol group oxidation can result in the transformation of protein products and some amino acid residues. The earliest sign of protein oxidation by free radicals is the oxidation of the -SH groups of amino acids. Thiols have interaction with most of the physiological oxidants and act as the essential antioxidant buffers [12]. Oxygen-free radicals cause lipid peroxidation in membranes, endothelial damage and can result in multiple organ failure. Another oxidation parameter that may be used as a perioperative ischemia marker is ischemia-modified albumin (IMA). Ischemia-reperfusion(I/R) injury, hypoxia, acidosis, and superoxide radical damage occur when the capacity of the albumin bind to metals by changing the structure of the N-terminal and IMA increases within minutes [13].

Surgery with anesthesia increases postoperative complications through endocrine, metabolic and immunological imbalance and increases morbidity and mortality incidences [14]. It is acknowledged that the tourniquet (TQ) application in extremity surgery causes I/R injury [9, 11, 15-18]. Despite the reduction in the operative time and intraoperative hemorrhage volume, incidences of local tissue and nerve damage as well as possibilities of venous stasis, endothelial dysfunction, and thromboembolism have been known [19]. There are investigations on anesthesia methods, I/R injury, stress hormones, and oxidation parameters in knee arthroplasty [12,15] but studies on the oxidative system in bilateral total knee arthroplasty (BTKA) are limited. Also, the occurrence of I/R injury and the preconditioning of ischemia in the first knee by TQ application in BTKA and its prevention in the second knee have been investigated [11, 20]. To the best of our knowledge, there has been no previous study on thiol homeostasis, which is a new biomarker of oxidative stress in bilateral knee arthroplasty.

In this study, we aimed to investigate the effect of TQ on ischemia-modified albumin (IMA) and thiol/disulfide homeostasis use in BTKA and unilateral total knee arthroplasty (UTKA) under combined spinal-epidural anesthesia (CSEA).

Material and Methods

The study protocol was approved by Uludag University School of Medicine's Ethics Committee (52588837-000/392, 201711/37). Written informed consent was obtained from patients. The study was conducted in accordance with the principles of the Declaration of Helsinki. This prospective study was carried out in a single center. The physician who evaluated the laboratory results was blinded to the study.

Patients aged 50-75 years with physical status I-III of the American Society of Anesthesiologists (ASA) for undergoing elective TKA were included in the study. The exclusion criteria were communication difficulties, preoperative cerebrovascular disease, renal or liver insufficiency, inflammatory or rheumatic disease, systemic infection or infection at the application site, body mass index >35, use of corticosteroids and antioxidant agents, and the likelihood of redo surgery. Patients who required conversion to general anesthesia were also excluded from the study.

Initially, 108 patients were recruited for the study. However, 5 refused to participate, 4 required intraoperative conversion to general anesthesia, 9 had to undergo redo surgery, and 28 had other reasons for exclusion from the study. Three of the remaining 62 patients had haemolysed serum samples and 2 had inadequate serum samples so that a total of 57 patients were included in the study after assignment to the UTKA (Group 1, n=33) and BTKA (Group 2, n=24) groups. The demographic data of the patients were recorded.

Anesthesia management

Routine intraoperative monitoring was applied to all cases. Heart rate (HR), mean blood pressure (MBP), peripheral oxygen saturation (SpO2) were recorded pre-operatively, at 5, 10, 15, 45, 60, 90, and 120 minutes following the regional intervention and after deflating the TQ. The intraoperative routine sedation consisted of midazolam (starting dosage: 0.5-1mg and titrating up to the maximal dose of 5mg), which then was followed by CSEA (Spinal epidural combined set, Egemen®, Turkey) performed at the L3-4 interspace. The patients were then administered intrathecally 3 ml of 0.5% hyperbaric bupivacaine (Busacain Heavy, Haver®, Istanbul, Turkey), and 0.25% bupivacaine (10-15ml) through an epidural catheter. The targeted hemodynamic values were defined as an increase or decrease in HR and MBP by more than 25% from baseline (16). After deflating the TQ, 3mg morphine HCl (Galen, Istanbul, Turkey) was administered through an epidural catheter for postoperative analgesia.

Operative procedure

All bilateral TKAs were performed by three surgeons. Thigh tourniquets were inflated before skin incision and deflated after skin closure. In all cases, TKA was completed on the first side before starting on the contralateral side. A medial parapatellar approach and cemented TKA components were used in all patients. The patella was not resurfaced and surgical drains were used in all patients.

Oxidation-Antioxidant measurements

Blood samples obtained preoperatively at 0 time (T0), 5 minutes after TQ deflation (T1), and at the postoperative 24 hours (T2) were kept at -80 ^{0}C until analysis. Serum samples obtained after centrifugation of the blood samples at 3600 rpm for 10 minutes were analyzed in the same session for native thiol, total thiol, disulfide, disulfide/native thiol ratio (SSSH), disulfide/total thiol percent ratio (SS/Total SH), native thiol/total thiol percent ratio (SH/Total SH), and IMA level.

A new spectrophotometric technique previously described

by Erel et al. [12] for the measurement of thiol/disulfide homeostasis was used. The IMA was measured in absorption units (ABSU) using the spectrophotometric method described by Bar-Or et al [21].

Statistical Analysis

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA). Continuous and ordinal variables were expressed as mean ± standard deviation, and nominal variables were expressed as frequency. The Kolmogorov-Smirnov test was used to determine the normality and homogeneity of the data distribution. Student's t-test was used for continuous variables with normal distribution when comparing the two groups. The Pearson chi-square test was used to detect intergroup differences on the basis of the categorical variables. The Mann-Whitney U test was used to compare two groups for continuous variables without a normal distribution. To assess the relationship between measurements of the mean serum albumin, IMA, native-thiol, total thiol, disulfide, SSSH, SS total SH, and SH total SH levels at different times, the paired t-test and Wilcoxon signed rank test were used. A p-value of <0.05 was considered statistically significant.

Results

Data of the 57 patients included in the study were analyzed statistically (Figure 1). The two groups did not differ significantly in terms of demographic features (Table 1). Durations of anesthesia, total TQ application, and hospital stay were significantly prolonged in the Group 2 (p<0.001, p=0.006 and p=0.035, respectively) (Table 1).

When comparing the data of the two groups at T0, T1 and T2, no statistically significant differences were determined in the levels of native thiol, total thiol, disulphide, SSSH, SS/Total SH, SH/Total SH and serum albumin (p>0.05) (Table 2).

In both groups, intra-group comparisons of serum total thiol, disulfide, SSSH, SS/TOTAL SH, and SH/TOTAL SH levels at T0-T1 and T0-T2 showed no significant alteration. Only serum native thiol was significantly reduced at T0-T1 in the Group 1 (p=0.022) (Table 2).

The IMA levels at T0 and T2 did not differ significantly between the two groups. Inter-group comparison of IMA levels showed a statistical increase at T1 in the Group 2 (p=0.002) (Table 2). When the intragroup IMA levels were compared between the two groups, the T0-T2 level change in the Group 1 and the T0-T1 and T0-T2 level changes in the Group 2 increased significantly (p=0.012 and p=0.001, p=0.01, respectively) (Table2).

Serum albumin values did not differ between the two groups. When assessed within the group, the levels were significantly reduced in both groups in the T0-T1 and T0-T2 intervals (p=0.027, p=0.005 and p<0.001, p<0.001, respectively) (Table2). HR and MBP did not differ significantly between the two groups. In the Group 1, comparison of the HR and MBP at T0 and T1 showed a statistically significant change (respectively, p=0.009 and p<0.001). In the Group 2, HR did not change at T0 and T1, but at 5 minutes after the first and second TQ deflations, the MBP measurements were significantly reduced (p<0.002, p=0.005, respectively) (Table 3).

Table 1. Demographic features of the patients

Variable	Group 1 (n=33)	Group 2 (n=24)	p-value
Age, years (mean±SD)	67.51±8.22	66.68±7.92	0.724
Gender, Female/Male, n	22/11	17/7	0.738
BMI	30.26±5.48	29.29±4.87	0.573
ASA I/II/III, n	6/21/6	5/18/1	0.281
Anaesthesia time, min (mean± SD)	127.90±35.95	202.86±61.55	<0.001 *
Tourniquet duration, min, First knee	112.09±25.77	110.61±44.68	0.551
Second knee	-	98.94±29.52	0.115
Tourniquet duration, min	112.09±27.77	199.55±68.56	0.006*
Length of hospital stay, days	5.18±2.09	5.91±1.64	0.035*

ASA: Physical status classification by American Society of Anesthesiologists; BMI: body mass index; SD: standard deviation; Group 1: unilateral TKA; Group 2: bilateral TKA; * Mann-Whitney U test

Table 2. Thiol/disulfide homeostasis and IMA levels

Paremeters		T0	T1	T2	P-value
Native thiol (µmol/L)	Group 1	258.39±47.48	235.24±39.62	254.±53.73	T0-T1=0.022¶ T0-T2=0.548
	Group 2	238.38±71.66	212.03±68.33	257.10±61.49	T0-T1=0.055 T0-T2=0.910
	P	0.242	0.441	0.903	
Total thiol (µmol/L)	Group 1	291.42±49.48	264.08±43.24	283.87±53.23	T0-T1=0.321 T0-T2=0.067
	Group 2	264.22±77.04	239.99 ±67.73	284.19±61.62	T0-T1=0.080 T0-T2=0.948
	P	0.136	0.128	0.869	
Disulphide-SS	Group 1	16.51±6.98	14.42±5.98	14.74±4.87	T0-T1=0.230 T0-T2=0.627
	Group 2	12.91±6.69	13.97±6.12	13.54±4.61	T0-T1=0.593 T0-T2=0.897
	P	0.072	0.254	0.295	
SSSH ratio	Group 1	6.59±3.08	6.22±2.55	6.29±4.14	T0-T1=0.702 T0-T2=0.992
	Group 2	5.64±2.88	7.58±5.65	5.89±4.63	T0-T1=0.115 T0-T2=0.977
	P	0.269	0.254	0.229	
SH/Total thiol ratio	Group 1	88.59±4.64	89.04±4.05	89.18±5.27	T0-T1=0.676 T0-T2=0.919
	Group 2	90.08±4.55	87.49±7.12	89.83±5.91	T0-T1=0.061 T0-T2=0.903
	P	0.260	0.337	0.253	
SS/Total thiol ratio	Group 1	5.70±2.32	5.47±2.02	5.40±2.63	T0-T1=0.674 T0-T2=0.918
	Group 2	4.95±2.27	6.25±3.56	5.04±2.87	T0-T1=0.09 T0-T2=0.871
	P	0.260	0.337	0.225	
IMA (ABSU)	Group 1	0.63±0.092	0.63±0.11	0.69±0.08	T0-T1=0.974 T0-T2=0.012¶
	Group 2	0.65±0.108	1.00±0.16	0.71±0.07	T0-T1=0.001¶ T0-T2=0.010¶
	P	0.537	0.002*	0.584	
Albumin	Group 1	3.83±0.66	3.37±0.73	3.30±0.51	T0-T1=0.027¶ T0-T2=0.005¶
	Group 2	3.95±0.48	3.28±0.72	3.11±0.47	T0-T1<0.001¶ T0-T2<0.001¶
	P	0.436	0.643	0.582	

IMA: Ischemia-modified albümin, Data presented show values at the moment of T0: preoperatively; T1: at the 5th minute after deflation (for second TQ in group2); T2: postoperative 24th hour. Group1: Unilateral TKA group; Group 2: bilateral TKA group. A *p* value of <0.05 is statistically significant. *Mann-Whitney U test; ¶ Paired Sample test.

Table 3. Comparisons between Group 1 and Group 2 of the HR and MBP data in the intra-operative period

	HR		MBP	
	Group 1	Group 2	Group 1	Group 2
Preoperative	77.96 ± 16.35	73.95 ± 12.35	113.96 ± 23.2	113.0 ± 20.04
Post-RI-5th min	71.30 ± 12.09	73.84 ± 13.35	92.84 ± 17.97	101.61± 15.08
10	70.66 ± 13.23	69.47 ± 13.18	92.48 ± 15.60	97.76 ± 14.42
15	69.69 ± 12.84	67.68 ± 10.00	88.96 ± 16.32	96.77 ± 11.59
30	66.54 ± 9.72	62.51 ± 8.23	89.33 ± 14.31	92.00 ± 14.55
45	64.39 ± 8.14	62.89 ± 11.33	89.00 ± 11.52	92.61 ± 15.07
60	64.87 ± 8.78	60.00 ± 11.38	92.48 ± 13.29	91.16 ± 13.72
90	66.06 ± 7.81	61.26 ± 8.69	90.34 ± 14.01	93.66 ± 15.18
120	66.44 ± 7.91	63.00 ± 8.16	92.44 ± 14.51	92.88 ± 14.29
1.Release tourniquet	68.63 ± 12.14*	69.38 ± 9.80	95.12 ± 14.50#	87.72 ± 17.01#
2.Release tourniquet	-	73.16 ± 12.64	-	95.77 ± 17.58#

Preoperative, at 5, 10, 15, 30, 45, 60, 90, 120. min after RI (regional intervention); HR: heart rate; MBP: mean blood pressure; Group 1:unilateralTKA group; Group 2: bilateral TKA group; between groups of p-value n.s. *Paired Sample test (intragroup T0-T1), #Wilcoxon Signed Ranks test, p<0.05

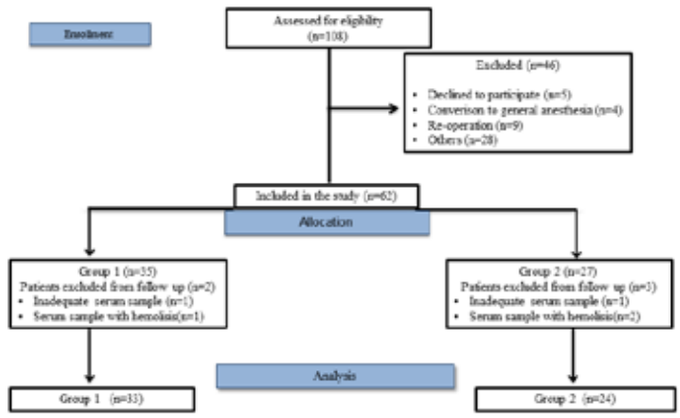

Figure 1. Flow chart of the study

Discussion

Although research on lower extremity operations including BTKA has increased in recent years, investigations on the effect of TKA on the oxidative system are of limited scope. In our study investigated the effect of BTKA on IMA levels and thiol-disulphide homeostasis. In the Group 2, immediately after the second TQ deflation, IMA levels exceeded those observed in the Group 1. Whereas the native thiol value was low in the Group1, it showed no significant alteration in the Group 2 after the second TQ deflation. The duration of anaesthesia, TQ application and hospital stay were longer for the Group 2.

The use of a tourniquet in TKA causes tissue ischaemia distal to the cuff, and after TQ deflation, reperfusion injury occurs and affects the systemic circulation [11]. Safe timing and pressure limits in TQ use are subjects of debate. Prolongued TQ application results in I/R with severer metabolic, cellular and microvascular changes and the release of oxygen free radicals [11]. There are studies in the literature on metabolic and oxidative parameters such as lactic acid, phosphocreatine, glutathione and amino acid changes in knee surgery [11, 15, 16-18, 20, 22]. Especially the effects of replacement therapies [11, 21] and anesthetic agents [16] on I/R are being investigated. There are limited clinical trials for reducing the I/R in TKA.

The thiol groups of proteins represent a diversified defense system against biochemical changes brought about by oxidative stress, with the thiols protected in the reduced state or as disulphides [23]. According to our knowledge, there has been no previous study on the thiol-disulphide homeostasis in TKA. The only study related to IMA was conducted by Kosucu et al. [16] in relation to I/R in arthroscopic knee surgery under inhalation, spinal and total intravenous anaesthesia (TIVA), when propofol intravenous anaesthesia was found to result in a lower level of I/R, and 1 and 6 hours after TQ deflation, the IMA levels were higher in patients under spinal anaesthesia. In our study, CSEA was used and IMA, which indicates acute ischaemia within minutes, was not distinctly affected at the 5th minute after TQ deflation in the UTKA group, but it was raised after 5 minutes in the BTKA group. There are differing recommendations in the literature for both the TQ and reperfusion intervals. However, most of the authors have recommended a duration of 1.5-2 hours [24,25]. The higher level of IMA in the Group 2 compared to the Group 1 may be related to the longer duration of TQ application.

Cheng et al. [15] investigated the reactive oxygen species (ROS) and lipid peroxidation in BTKA under spinal anaesthesia. At 5 and 20 minutes after the first TQ deflation and the resultant reperfusion, an increase in ROS production was observed, whereas 20 minutes after the second reperfusion, it returned to normality and no significant change was determined in lipid peroxidation. Lee et al. [20] reported that high doses of vitamin C helped prevent haemodynamic instability and ROS production in BTKA. Also, they observed in the control group that malondialdehyde levels were raised at 5t and the 20 minutes after TQ deflation as compared to the level after administration of anesthesia, but a significant change did not occur after the second TQ deflation. In both of these cited studies, by Cheng et al. [15] and Lee et al. [20], the oxidation parameters increased after the first TQ deflation, but did not change at the 20th minute after the second TQ deflation [15,20]. In BTKA cases, after intervention on the first knee, increased biochemical parameters of postoperative oxidative stress and muscle injury were detected along with increased levels of serum malondialdehyde, creatine kinase and lactic dehydrogenase compared to the second knee. In our study, native thiol level decreased at 5 minutes after the TQ deflation only in the UTKA patients, while the other values related to the thiol-disulfide homeostasis did not change. Although we did not determine serum parameters after the intervention on the first knee in the BTKA cases, native thiol values did not change after reperfusion in the second knee, which may be due to ischemic preconditioning effect. Ischemic preconditioning has shown that any injury occurring after an ischaemic event in another location in the body increases ischaemic tolerance of the tissue and reduces oxidative stress, inflammation, and apoptosis in the tissue [22, 25]. It is believed that a natural protective mechanism augmenting the tolerance to prolonged ischemia is activated in tissue after exposure to short-term ischemia and

reperfusion.

Hemodynamically, in both Group 1 and Group 2, the MBP values differed significantly at the beginning and after the first TQ deflation, and this was also observed after the second TQ deflation. HR also changed significantly in Group 1, which may be due to the presence of more patients with ASA 2 and 3 classification in this group, although not statistically significant. The limitations of our study include being single centered, not investigating postoperative complications and the postoperative antioxidant status in the long term and also after the intervention on the first knee in the BTKA Group 2, and no cost analysis.

Conclusion:

Bilateral TKA under CSEA does not adversely affect thiol homeostasis and hemodynamics. Elevated IMA levels immediately after TQ deflation indicate that early-stage ischemia is more significant and critical. IMA and thiol homeostasis are similarly affected at the postoperative 24th hour. Although BTKA under a single anesthesia session is advantageous for patients with compatible general health, the durations of the operation and of hospital stay are extended. We believe that BTKA studies with a larger number of patients comparing different anesthesia methods and including cost analyses will be beneficial in the long term.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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